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Statistical analysis plan (SAP) for the CONEX trial

Exploring the Effect of Space and Place on Response to Exercise Therapy for Knee and Hip Pain; a double-blind randomised controlled clinical trial.

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Table of contents

1. Study synopsis	3
2. Study design	3
2.1. Sample size	4
2.2. Randomisation and blinding	5
3. Study population	5
4. Study objectives and outcomes.....	5
4.1. Primary objective.....	5
4.2. Primary outcome	6
4.3. Secondary objectives and outcomes	6
5. Implementation of statistical analysis plan	6
6. Statistical analysis.....	7
6.1. Primary endpoint.....	7
6.2. Secondary endpoints	8
6.3. Protocol deviations.....	8
7. Tables and figures.....	9
8. References	10

1. Study synopsis

The physical environment affects the persons in it and may potentially be of significance for health and treatment effects¹⁻³. Many rehabilitation and hospital exercise facilities are today located in large rooms in basements or other windowless rooms with poor acoustics, not designed for optimal exercise therapy delivery.

Previous studies on the role of physical environments on health outcomes have been conducted in hospital environments. These studies have reported that factors such as noise, daylight deprivation and light intensity may increase stress and pain level, reduce patient satisfaction and affect length of hospital stay²⁻⁶. Consequently, inappropriate physical environment is known to affect health in hospitalized patients. Similarly, inappropriate physical environments for exercise may affect participants negatively.

Exercise is recommended as a life-long treatment for chronic diseases as musculoskeletal disorders, including hip and knee osteoarthritis (OA) and joint pain. Large variation in effect is observed across studies and treatment effects vary from small to large^{7,8}.

Theoretically, an enhanced physical environment may correspondingly create a positive atmosphere, enhance communication during exercise and potentially improve exercise performance, compliance and perceived wellbeing⁹.

The primary study aim is to investigate the effect of exercising in a contextually enhanced physical environment compared to a standard exercise environment for people with knee or hip pain as measured by participants' global perceived effect (GPE) assessed after 8 weeks of exercise.

The study tests the hypothesis that participants exercising according to a standardised program in a contextually enhanced physical environment will report greater improvement from exercise compared to participants following the same exercising program in a standard physical environment.

A study protocol describing rationale, design, methods, outcomes and endpoints has been published¹⁰.

2. Study design

This study is designed as a 3-armed randomised controlled clinical trial. Participants are randomised to three intervention groups; exercise in a context enhanced physical environment (EX+ROOM), exercise in a standard physical environment (EX) or waiting list (WL) (Figure 1).

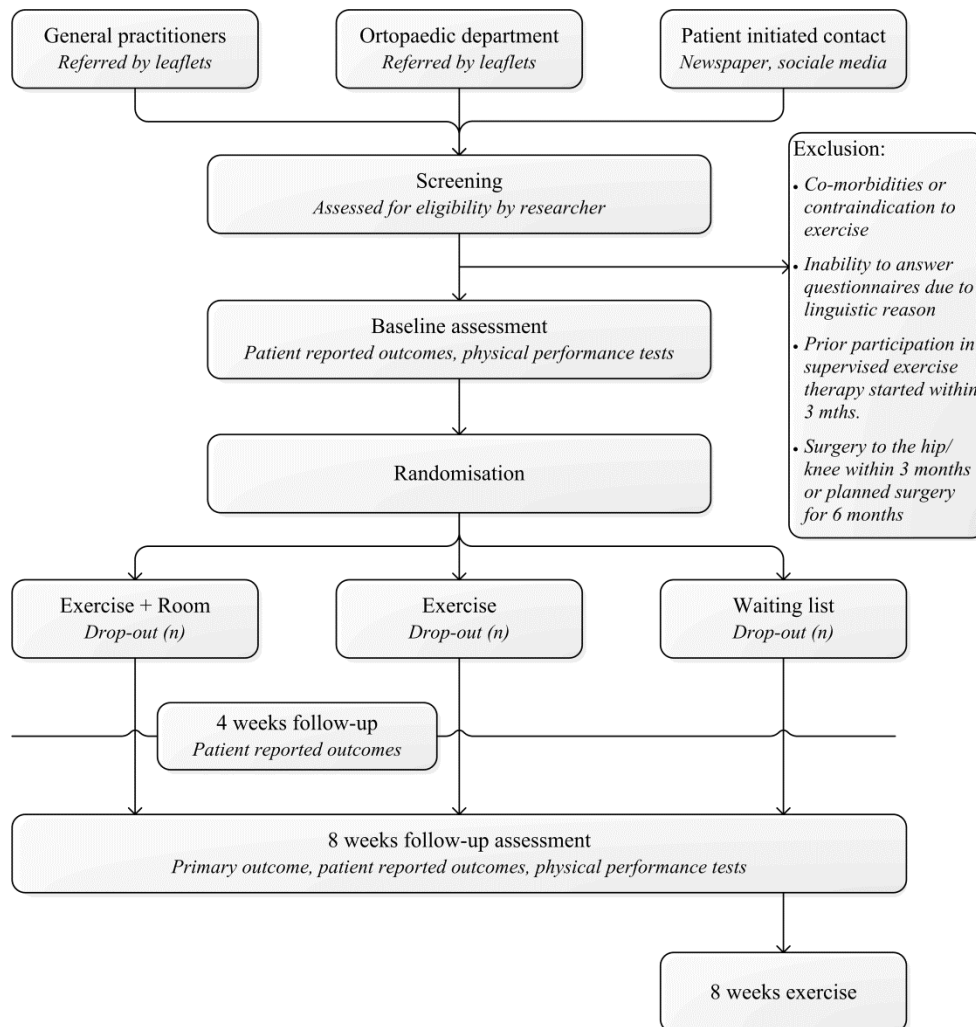


Figure 1: Flowchart during screening, inclusion and completion of the CONEX trial

2.1. Sample size

This study is designed as a superiority trial with three groups (EX+ROOM, EX and WL). This study is the first study to investigate the context effect of an enhanced physical environment on exercise therapy. Therefore information regarding SD and effect size from this sort of intervention from previous studies has not been available. The power calculation for this study is consequently based on feasibility and results in a sample size of 100 participants with a 2:2:1 allocation, therefore 40 participants are randomised to EX+ROOM and EX groups, and 20 participants to the WL group.

The primary analysis compares the EX+ROOM and EX groups. With 40 subjects in each of the two exercise groups, we are able to detect a difference of 0.75 on the GPE scale ranging from -3 to 3 with a standard deviation of 1.2 (corresponding to a standardized response mean of 0.62), a p-value of 0.05 and a power of 80%.

The WL is been omitted from the primary analysis for two reasons. Firstly, The WL enables us to address the question of whether a potential treatment effect is caused by either regression towards the mean or spontaneous remission¹¹. The WL is an untreated control group, which acts a reference of the natural course of disease during the 8-week intervention period. Any difference between the WL group and either of the EX+ROOM or EX group will signify a genuine treatment effect that cannot be caused by natural

course of disease or regression towards the mean as represented by the WL group¹². Secondly, as the primary aim is to investigate if there is an additive effect of the physical environment on the effect of exercise, then this effect will be detected as a difference between the EX+ROOM and EX groups. Thus, the WL group is excluded from the primary analysis. The WL design has been used in studies investigating the context effect originating from the patient-practitioner relationship during treatment^{13, 14}.

2.2. Randomisation and blinding

The randomisation sequence is computer-generated and prepared by a statistician with no clinical involvement in the conduct of the trial. To avoid imbalances in treatment allocation among people with knee and hip pain, two block randomisation lists has been computer-generated. Block size is kept secret to maintain blinding; each block consisting of either 5 or 10. Randomisation is performed immediately after baseline assessment and is administered by a research coordinator, not otherwise involved in the study. Participants are consecutively assigned and given a numbered, sealed, opaque envelope entailing treatment allocation.

Participants are blinded to the true study aim in order to avoid excess focus on the physical environment, which potentially could exaggerate a context effects originating from the physical environment. The instructors supervising the exercise sessions are correspondingly not informed of the true aim of the study. However, they are aware that the exercise is performed in different rooms as they supervised sessions in both rooms. The instructors are informed that the different exercise rooms are necessary for practical and logistic reasons. Blinding of instructors is implemented to eliminate any bias, which can be caused by any changes in behaviour caused by the two exercise environments if the supervising instructors are familiar with the specific aim of the study. The primary investigator conducting baseline and follow-up testing is blinded to treatment allocation. At follow-up testing participants are instructed to not to speak to the assessor about the intervention to ensure blinded assessment.

3. Study population

Recruitment strategies, screening and inclusion processes are described in the published study protocol¹⁰. Eligible participants are 35 years or older, self-reporting persisting knee and/or hip pain within the last 3 months and are willing and able to attend exercise therapy twice weekly at the University of Southern Denmark, Odense M.

Exclusion criteria are: 1) Co-morbidities or contraindication prohibiting participation in exercise therapy; 2) Inability to answer questionnaires or to speak, read or understand Danish; 3) Already participating in exercise therapy, defined as an exercise program supervised by a physiotherapist, or systematic training with duration of 6 weeks or more, started within 3 months to inclusion, and aimed specifically at relieving knee or hip joint problems; 4) Having had surgery to the hip/knee within the last 3 months or waiting for joint surgery in the coming 6 months.

4. Study objectives and outcomes.

All outcomes are obtained from participants at baseline and 8 week follow-up. Additionally a 4-week follow-up is administered via an online survey, where all questionnaires, NRS pain and registration of adverse event are included.

4.1. Primary objective

The study aim is to investigate the effect of exercising for 8 weeks in a contextually enhanced physical environment compared to a standard physical environment for people with knee or hip pain. The primary outcome is participants' GPE score assessed at 8 weeks. The primary objective is to compare mean GPE score at 8 weeks follow-up between the EX+ROOM and EX.

We hypothesize that, participants exercising according to a standardised program in a contextually enhanced physical environment will report greater improvement from exercise compared to participants following the same exercising program in a standard physical environment as measured by participants' GPE. Further, we expect that the two exercise groups (EX+ROOM and EX) will be superior to a passive waiting list, so a graded relationship is evident.

4.2. Primary outcome

Participants are asked to respond to the following global perceived effect question; "Compared to before you entered the study, how are your knee/hip problems now?" on a 7-point Likert scale. The GPE scale ranges from 'markedly worse' through 'no change' to 'markedly improved'. GPE is a reliable method for measuring the effect of clinical interventions¹⁵⁻¹⁷. It has prior been used in studies investigating contextual effect of treatment¹³.

There are different arguments for choosing participant's GPE as the primary outcome. The GPE allows for a broader perception of improvement, as the individual participant is able to define improvement on the parameter of the disease which they find important compared to an outcome measuring one specific dimension of health¹⁵. GPE are intuitively easy for participants to understand and answer¹⁷. This has been argued to increase the relevance of information from clinical trials into clinical practice as the GPE reflects changes as perceived by the patient thereby giving it clinical relevance¹⁷.

Further as this study is the first to assess the effect of the physical environment on the effect of exercise we found no support in the literature to choose one dimension of health over another in respect to where such an effect from the physical surrounding might be evident. Consequently, participants GPE was chosen to increase the probability of detecting improvement in participants.

Some authors have suggested that GPE ratings are influenced by current health status¹⁷, others that the participant's GPE may not reflect the same magnitude of change as objective measures but bare closer relation to changes in self-reported outcomes¹⁸. However, a study on the correlation between transition ratings, and pre and post score of quality of life questionnaires showed a correlation of 0.8 between the change score of the questionnaire and the transition ratings suggesting that transition scales, such as global perceived effect, are valid for detecting changes and can be used in clinical trials as primary outcome measures¹⁶.

4.3. Secondary objectives and outcomes

The secondary objective is to compare difference from baseline to 8 weeks follow-up (including 4 week follow-ups where available) between the EX+ROOM and EX groups in all secondary outcomes. All outcomes are described in detail in the published protocol¹⁰.

5. Implementation of statistical analysis plan

This statistical analysis plan will be a working description to the parties performing the statistical analyses. All analyses regarding the primary outcome, participants' GPE score, will be performed by the third party. None of the investigators involved in this trial will be involved in these analyses.

The secondary outcomes; KOOS/HOOS subscales, 4x10m fast-paced walk, chair stands pr. 30 sec and participants' satisfaction with the physical environment will be analysed by the third party conducting the primary analysis. The third party will perform analyses blinded to treatment allocation.

All other analyses on all other secondary outcomes will be performed by the primary investigator post unblinding the treatment allocation.

Implementation of the statistical analysis plan will be conducted as follows:

- 1) A structure for the dataset will be outlined in collaboration between the third party performing the analysis and the principal investigator.
- 2) The research coordinator will code each treatment arm into "treatment A", "treatment B" and "treatment C". Thereby the party performing the statistical analyses and all investigators involved in the study will be blinded from treatment allocation during the analysis.
- 3) Blinded data will be delivered to the third party according to the agreed upon structure for the dataset.
- 4) Results will be presented to the author group of the study. The author group (as listed on the front page) will draft two interpretation scenarios on the basis of the primary outcome data, i.e. comparing treatment A with treatment B. One assuming that group A will be the EX+ROOM group and another assuming that A will be the EX group. Intervention groups will be allocated arbitrary names (A or B). The two interpretations will be discussed and consensus will be reached regarding clinical interpretation of the results. When agreed upon all members of the author group will approve and sign the interpretations as suggested by Järvinen et al.¹⁹ Only hereafter will the group allocation be unblinded.

6. Statistical analysis

All three intervention groups (EX+ROOM, EX and WL) will be examined for comparability at baseline with respect to demographic factors using analysis of variance (ANOVA) and Chi-squared test as appropriate.

6.1. Primary endpoint

The GPE data will be checked for normality by visual inspection of histograms and quantile-quantile plot (probability plot) and a test for unequal variance between groups.

A Student's unpaired t-test comparing GPE scores between the EX+ROOM intervention group with EX intervention group at the 8-week follow-up is performed as primary analysis, to test the *hypothesis*; that participants exercising in the contextually enhanced environment (EX+ROOM) will experience larger effect than the participants exercising in the standard exercise environment (EX).

If the assumption of normality in the GPE data is not supported, the Bonnet-Price median test will be conducted as a non-parametric alternative.

As described earlier, the WL intervention group is considered a reference group describing the natural progression of disease for the included study population and is therefore not included in the primary analysis. However, to check the general assumption, that exercise is more effective than no intervention, two analyses applying the unpaired t-test are conducted to compare the exercise groups with the waiting list, i.e. EX+ROOM vs. WL and EX vs. WL.

A per-protocol analysis is conducted including only those with good compliance with the exercise intervention (participated in at least 12 of 16 sessions) in the EX+ROOM and EX groups, respectively.

6.2. Secondary endpoints

All secondary outcomes will be checked for normality by visual inspection of histograms and quantile-quantile plot (probability plot) and test for unequal variance between groups.

The secondary outcomes, the patient reported outcomes, KOOS/HOOS; ASES, SF-36 and functional performance tests are analysed as repeated measures with a multiple regression analysis using a mixed model. In this model, participants are considered as random effects and time-points and group allocation are fixed effects. All available data points are included in the model. Patient reported outcomes are obtained at baseline, 4 weeks and 8 weeks, for functional performance test assessments are available from baseline to 8 week follow-up. As for the primary analysis, only the EX+ROOM and EX groups are compared.

6.3. Protocol deviations and clarifications

The choices for fixed effects in the repeated measures mixed model for analysis of the secondary outcomes have been revised substituting sex, age and joint as fixed effect for time and group.

The strategy for handling any missing data in the GPA data has been clarified in the statistical analysis plan compared to published study protocol.

7. Tables and figures

Table 1: Baseline characteristics

Baseline characteristics	EX+ROOM	EX	WL
Gender (f/m)			
Joint (k/h)			
Height (cm)			
Weight (kg)			
Age (yrs.)			
Marital status			
Educational level			
Employment status			
Alcohol consumption			
Smoking			
Physical activity level at work and leisure			
Pain, NRS, index joint			
Primary outcome			
Global Perceived Effect			
Secondary outcomes			
Patient reported outcomes			
KOOS/HOOS			
Pain			
Symptoms			
ADL			
Sport/Rec			
QOL			
SF-36			
Physical component summary			
Mental component summary			
Modified Arthritis Self-Efficacy Scale			
Pain scale			
Symptom scale			
Patient Acceptable Symptom State (y/n)			
Patient satisfaction (5 point Likert scales).			
Stress (100 mm VAS)			
Objective physical function tests			
Single-limb mini squat			
Knee bends/30 sec. (no.)			
Chair stands/30 sec. (no.)			
Walking test, 40 m fast paced. (sec)			
One-leg hop of distance (cm)			
Aerobic capacity (ml O ₂ /min/kg)			
Isometric strength hip abduction (Nm)			
Isometric strength knee extension (Nm)			

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